Aus der Universitäts-Kinderklinik (Jennerspital) Bern

Direktor: Prof. Dr. E. Glanzmann

GARGOYLISM

(Review of the Literature and Report of one Case)

INAUGURAL-DISSERTATION

zur

Erlangung der Doktorwürde

der Medizinischen Fakultät

der Universität Bern

vorgelegt von

Merwin Geffen

von Utica, New York, USA

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HISTORICAL REVIEW OF THE DISEASE

The earliest account of a reference to Gargoylism may be accredited to Berkhan (1907) and Hunter (1917). However, the disease was probably first observed by Dr. John Thompson of the Royal Edinburgh Hospital. After his first patient, he called it "Johnny Mc L ....'s Disease." Among Johnnie's siblings, he found two similar cases, one in 1908 and one in 1913.

In 1919, G. Hurler described in a report of a disease in two children a separate syndrome of skeletal deformities, slight clouding of the corneas, hepatosplenomegalie and mental deficiency. This picture came to be known as the Pfaundler-Hurler Disease. In the "Ergänzungsband zum Handbuch der Kinderkrankheiten", the disease was further studied and described and became additionally known as Dysostosis multiplex. Because of the remarkable similiarity of the facies revealed by these patients to the gargoyls found on Gothic cathedrals, Ellis, Sheldon and Capon, in 1936, added the further title of Gargoylism to the disease. Washington, in a study of the pathology seen in four of his own cases, offered the suggestion, as explanation of the skeletal abnormalities which he observed, that the disease was primarily a chondrodystrophy. Since he believed that the infiltrating substance seen in the histological examination of his cases was a lipid material, he coined the term lipochondrodystrophy. The first example of the disease to be reported in the United States was by Putnam and Pelhan, in 1925.

PATHOLOGY

According to G.L. Henderson et al., until 1951 only 12 detailed and 10 incomplete pathological studies of Gargoylism had been reported. In addition, several biopsy reports were also available. Perhaps the most important and most welcomed addition to the literature of the pathology of this curious disease was the detailed study by Lindsay, Reilly, Gotham and Skahen in 1948 of the pathology of 12 cases. Before this, a scarcity of only six reasonably complete cases had been reported by Reilly (1935), Kressler and Aegerter (1938), (first detailed account of a typical case), De Lange (1942), Kny (1942), Gerlings, De Kleyn and Littenga (1944), and Strauss (1948). Henderson et al. have since contributed a complete autopsy report of one case.

In 1934, Tuthill reported the examination of the brain from a patient originally described by Hurler. Ashby, Stewart and Watkins report of two cases was also mainly a description of the nervous system. Other incomplete reports have been offered by Stöckel (1941), Wolff (1942), Nja (1945), Mager (1950), and Jervis (1950).

Biopsy examinations have been described by Ellis in 1937 (liver and spleen); Reilly in 1935 (liver); Debré, Marie and Thieffry in 1946 (liver); Höra in 1939 (bone); Schmidt in 1942 (bone), and Henderson et al. in 1951 (liver and spleen).

Henderson et al. reported in a review of the pathological findings of cases of Gargoylism the following discussion:

Of 23 macroscopical descriptions of the liver, 16 were found enlarged. The others were normal, and one was even smaller than normal. The cut surface was usually described as showing an abnormal pallor. The histological picture most frequently revealed a disturbance of the normal cord arrangement of the cells with increased connective tissue in the portal spaces. In a minority of cases, irregular strands of hyaline connective tissue were seen throughout the parenchyma. The parenchymal cells were generally enlarged, with vesicular or foamy cytoplasm. In many cases, the cells revealed an eccentric nuclei. Only 3 of the 24 cases reported revealed no histological abnormalities. Schwartz and Gagne reported a case of Gargoylism with cirrhosis of the liver and portal congestion, which resulted in profuse haematemesis, melaena and death of the patient.

Approximately 3/4 of the pathological descriptions of the spleen revealed an enlargement with considerable variation in its consistancy. Most striking was the histological finding of an enlargement of the reticulo-endothelial cells lining the sinusoids and the presence of many large mononuclear cells in the intersinusoidal spaces. Both types of cells were distended and vacuolated. 5 of the 17 descriptions of the spleen were reported normal.

The brain was frequently enlarged with 9 of the 22 reports revealing a symmetrical internal hydrocephalus; other inconsistant gross findings were listed as:

a) small perivascular cysts in the white matter containing mucoid-like material;
b) moderate degree of atrophy of the white matter;
c) widening of the cortical layers of the cerebral hemispheres with scattered, numerous, small, yellow-opaque zones of softening;
d) indistinct outline of the cortical layers;
e) ependymal thickening with brown pigmentation, edema and fibrinous exudation.

Microscopically, changes appeared in all but 2 of the 20 histological studies reported. Less than 1/2 of the cases showed changes in the cortical cytoarchitecture, with loss of columnar arrangement and a reduction of the cortical nerve cells. Pathological changes of the cortical nerve cells were seen in almost all instances. Most of the cells appeared swollen with eccentrically displaced nuclei. The cytoplasm, sometimes vesicular, consisted of greyish granular non-staining material. The Nissl substance in many cells was greatly reduced, and, in some instances,

had even disappeared. Interspersed among these changes, both normal and disintergrating cells could be seen. The dendrites were usually wide and distended. Some had disappeared. The axon was less abnormally affected. Not all parts of the central nervous system were equally affected by the changes cited above, although almost all parts, as a rule, revealed some abnormal cells. The areas of special predilection in order of frequency were the cortex, basal nuclei, nuclei of the brain stem and the cerebellum. Other structures showing less frequent changes were the Purkinje cells, the external granular layer, the dentate nucleus and both the anterior and posterior horn cells. Of the 8 cases which reported changes in the myelin sheath, 5 showed demyelination. Reference to the glial elements was rather rare, although Lindsay described an excess of glial and microglial cells in the cortical white matter and changes in the glial cells similar to those of the nerve cells, but of lesser severity. Green further described gliosis in both the grey and white matter of the cortex, the basal ganglia and the spinal cord. More significant, however, was the observation that the astrocytes and oligodendroglia might reveal abundant, clear, vacuolated cytoplasm similar to that seen in the nerve cell. Sympathetic ganglia showed cellular changes similar to those found in the other parts of the central nervous system. While a variety of inconsistant gross changes have been observed in the meninges, the most characteristic and consistant features were found in the histological evidence of a large number of macrophage cells of either elongated structure with small, darkly staining nuclei and abundant brightly staining reticulated cytoplasm or of round structure with pleomorphic nuclei and abundant honeycombed cytoplasm. Sheets of foamy cells were also noted.

The pathology of the bone revealed a dysostosis. Schmidt was the first to describe the features of swelling and vacuolation of cartilage cells. He found a deficient growth of the epiphyseal cartilage and a deficient development of the marrow room. In certain areas of the epiphyseal line, the normal arrangement of the cartilage was lacking. The cartilage cells were seen to lie in a disorientated pattern or in columns of only 2 to 3 cells. The enchondral bone development, especially in outer portions of the cortex, was deficient, and there was an extremely small intensity of resorption and apposition of the endoperiostial bone. Kny found similar changes. Lindsay et al. demonstrated in 8 cases fairly uniform changes of swelling and vesiculation of cartilage cells. The cartilage cells, especially in the costochondral junctions, showed more than normal vesicular and granular cytoplasm. The cells filled the lacunar spaces in the cartilagenous matrix. Both the oesteocytes and certain of the connection tissue cells in the outer layer of the somewhat thickened periosteum showed similar changes. Of particular interest was the histological finding of abnormal lumbar vertebrae in 2 of the reported cases. These

showed vertebrae with irregular epiphyseal lines. The cellular changes already described were evidenced in the oesteocytes, cartilage cells and periostial cells. Osteoblastic activity was lacking on the bony trabeculae and the unusually thin layer of cortical bone forming the anterior portion of the vertebral body gave the appearance to the vertebrae of being anteriorly collapsed. In 3 cases the separation into inner and outer tables was lacking.

Cordes and Hogan, in a report of 3 cases, stated that in over 75 % of cases, bilateral corneal clouding was present, usually appearing before the age of three. The corneas were described as having a ground glass appearance. Indications of injection of the conjunctive and vascularization of the cornea were lacking. Split lamp examination revealed, at the onset of the disorder, small, uniformly distributed, non-crystalline and only slightly refractible yellow-grey dots in the middle and deeper layers of the cornea. Later, the distribution became more general. The disturbance, reaching a certain degree of opacity, remained unaffected. Degenerative changes in this material have not been reported. Histological studies revealed changes in both the normal tissue cells and phagocytes. Many of these cells were swollen, and appeared globular or spindle shaped, and were vacuolated and granular. The phagocytic cells infiltrated to Bowman's membrane which accounted for its ultimate rupture. Further, eye changes were seen in the iris, ciliary body, choroid and the nerve cells in the nuclear layer of the retina. These changes also displayed similar cellular disturbances. Wettler substantiated those findings. He further observed that the ability of the pupils to dilate was decreased. Opticus atrophy and even amatio retinae were observed. Ocular tension in most cases was normal, but occasionally was increased.

Pathological changes of the heart were observed in almost all autopsy reports. Enlargement, hypertrophied left ventricles and abnormalities of the heart values especially of the mitral and tricuspid were the most consistant notable features. Less frequent changes, such as endocardial thickenings and opacities, coronary defects and myocardial pallor were described. Again, the gross appearance of the various lesions could be accredited to the histological evidence of the swollen mononuclear cells of the type seen in other tissues.

Similarly, pathological changes found in the blood vessels of these patients, especially of the aorta, coronary and cerebral arteries, were accountable to the presence of these cellular elements within their walls and by an accompanying fibrosis.

Pathological changes involving the deposition of an abnormal substance in certain cells and interstitial tissues of the kidney were also reported. The storage phenomenon appeared to be present in the glomeruli often associated with thickening

of the glomerular basement membrane. Vacuolation was also observed in the tubular cells, and some of the renal connective tissue was altered.

The gross anatomy of the gonads, in all reported cases, appeared normal. The majority of the male cases exhibited hydrocoele. 2 cases were reported with bilateral hydrocoele. Histologically, many cases revealed vesiculation of cells in either the parenchymal or intersestial cells or both. Small groups of foam cells were present in the ovarial stroma of one reported case.

One case of Gargoylism exhibited characteristic vacuolation of cells in the prostate and other parts of the urinary tract.

Lymph nodes were enlarged in many cases; the abdominal more frequently than the tracheobronchial. Microscopic investigation revealed small and indistinct follicles. Many of the reticuloendothelial cells were enlarged and vesicular. The sinusoids appeared generally broader than normal.

Of the 13 cases reporting the pathology of the pituitary gland, 6 were found to be enlarged. The sella turcica on the other hand was described as enlarged in 13 of the 14 cases reported. The anterior lobe showed vacuolation in most cells, especially the chromophobe cells. The glial cells revealed vacuolation, and fragmentation of the glial fibers was evident in certain cases.

The thyroid gland was enlarged in only one reported case of Gargoylism. In 8 of the 13 histological reports, the gland appeared normal. The lesions of the other 5 were not consistant and could not be said to be characteristic of the changes in Gargoylism. This finding is of particular interest because of certain similarities between the clinical pictures of this disease and thyroid deficiency.

Further, the thymus gland, adrenals, lung and pleura, alimentary tract and the perivascular connective tissue all showed rather inconsistant changes characterized by the cellular lesions evidenced in those organs already described.

Alopecia was noted. Epithelial cells of the surface of the mucosa and skin, as well as of the hair follicles and sweat glands, showed vacuolation.

One case revealed an abnormal bone marrow with infiltration by macrophages and connective tissue elements of the marrow spaces of the teeth, mandible and the petrous portion of the temporal bone.

CELLULAR LESIONS

A review of the pathology of Gargoylism makes it apparent that the disease is unquestionably one of abnormal storage in which all tissues of the body may be affected. It may further be seen that the signs and symptoms of the disease may be explained as an extensive storage reaction. The liver, spleen and brain are invariably affected in typical cases, whereas certain of the other body organs and tissues may reveal no abnormalities. All affected tissues show essentially the similar features of cytoplasmic swelling with the frequently accompanying enlargement of the cell. The cytoplasm may appear either clear, granular or vacuolated. The altered cytoplasm may vary in different situations and give a variety of histological pictures to the individually affected cells. Epithelial cells as well as reticulo-endothelial cells, nerve cells and mesodermal connective tissue are involved.

Lindsay et al. assumed that the intercellular substance derived from altered connective tissue elements would also be expected to be abnormal. Abnormal microscopic appearance of the matrixes in many situations; loss of the normal fibrillary characteristics of the altered connective tissue which often appeared homogenous and swollen; poorly formed osteomucin and chondromucin; increased amounts of collagenous intercellular substance associated with storage phenomenon in the fibrocytic cells in many tissues, and lack of normal osteoplastic activity with interruption of the continuity of the epiphyseal lines by groups of foam cells appear to be ample proof for that assumption.

Although it is apparent that Gargoylism is a metabolic disorder, the abnormal deposit in question and the way in which it is stored have been the subjects of considerable speculation. Tuthill, in 1934, having noticed the striking histological lesions of the brain in the case which he described, concluded that these lesions were characteristic of juvenile amaurotic idiocy. Ashby also found that the intracellular substance stained in a manner similar to that seen in Tay-Sach's idiocy. Reilly, in 1935, and Ashby, Stewart and Watkins, in 1937, suggested that the substance in question was a cerebroside, either kerasin or phrenosin, or a mixture of both. In 1936, Ellis, Wheldon and Capon based their belief that Gargoylism was a disease of lipid storage on the analogy and similiarities to certain other established diseases of lipid storage. Kressler and Aegerter, in 1938, presented the first indications of the systemic distribution of the disease. In their case, the disturbed cellular elements gave negative reactions for glycogen and lipid stains; were positive only in those cells normally containing fat. The attempts made by the above authors did not yield consistant results. They were unable to identify the exact nature of the substance, even though investigation of the deposit was carried through with a variety of methods of fixation and staining.

Because of the persistent difficulties to demonstrate the lipid nature of the unknown substance, the doubt arose that the disease was a lipodosis.

De Lange, in 1944, and Strauss, in 1947, noted that the substance accumulating in the cells might be a glycogen. Lindsay et al. indicated that the glycogen storage process in Gargoylism was not associated with demonstrable alterations in carbohydrate metabolism as in true glycogenesis (von Gierke's disease), and presented the thesis that the excessive cellular carbohydrate may be metabolically inactive and may not be involved in the turn over of an otherwise normal carbohydrate metabolism. They suggested that the combination of glycogen with a protein as a glycoprotein or mucoprotein stored in the cytoplasm of the cells perhaps could explain the inconsistent histochemical staining reactions recorded to that date.

The quantitative differential lipid analysis of the liver and spleen done by Henderson et al. in 1951, in one of their cases, showed values within the normal range. They demonstrated the absence of an increase of any lipid fraction in a typical case of Gargoylism. The disease was considered by these workers as no longer being one of abnormal lipid storage resulting from an abnormal intracellular lipid metabolism. They believed that there was little doubt that staining reactions might give a very misleading impression of the amount of tissue metabolite present in organs; only quantitative chemical methods could give a reliable indication of an increase or decrease. They felt that, unfortunately, Lindsay et al. based their conclusions on qualitative staining methods only. Without the support of quantitative chemical analyses of the stained substances in the affected organs, and in the corresponding organs of control, their interesting hypothesis remains unproved. They concluded that there was no satisfactory evidence that the deposit in Gargoylism was either a lipid or pure glycogen and that the pathogenesis of the disease remained unproved. They felt that further biochemical studies should demonstrate whether the substance is a glycoprotein or mucoprotein as had been suggested.

Dawson believed that a defect in the enzymes concerned with some phase of the metabolism of mucopolysaccharides leads to the accumulation of this substance in connective tissues. However, intermediary metabolism of mucopolysaccharides is too little understood to define Gargoylism precisely.

CLINICAL FINDINGS

Gertrude Hurler, in 1919, first described the clinical syndrome seen in two children with skeletal deformities, idiocy, clouding of the corneas and hepatosplenomegalie. Since then, over 150 cases have been described with contrasting diagnosis,

description and catagorizing of the disease. This may be accredited to the relative scarcity of and lack of familiarity with the earlier cases. Also, the extensive symptomatology with considerable variations in the individual symptoms which the disease manifests, may be further offered as a possible explanation of that state of affairs.

The symptomatology of Gargoylism creates a clinical picture which may be kaleidoscopic in its proportions. Diagnosis is based upon a variety of clinical components, each not always present in all cases. Paradoxically, however, while the signs and symptoms are manifold and varying, they produce a unique and characteristic clinical entity. When all the major manifestations are present, one or two of them are usually less marked than the others; and one or more of its elements may be missing entirely when all the others are pronounced.

The findings described in a variety of reported cases have revealed the following multitude of signs and symptoms.

The skull is enlarged and has been described as dolichocephalic, scaphilocephalic, brachycephalic, oxycephalic or hydrocephalic in form. The calvarum may be thicker or thinner than normal. The fontanelles may exhibit delayed closure, and the sutures may be palpated as boney ridges. Further, a boney ridge may be palpated from the bridge of the nose up to the beginning of the scalp. The supraorbital ridges are distinctly marked and prominent and may show a bushy hypertrichosis of the eyebrows. The eyelids may be thickened and heavy, and ptosis has been described. Exophthalmus, divergent squint and optic atrophy have also been reported (Crouzon's Disease). The ears may be large and set low on the head. The bridge of the nose is depressed and hypertelorismus present. The latter sign describes a craniofacial deformity with enlargement of the sphenoid bone; a greater than normal breadth of the bridge of the nose with a corresponding great width between the eyes. The nose is wide, flat, and thick, and presents big nostrils. Corneal dystrophy is marked by a diffuse parenchymal clouding. Dentation may be delayed, and the teeth may be small and grey, as well as widely spaced. Hypertrophy of the alveolar ridge of the upper maxilla and the upper gums has also been noted. The tip of the nose may be flat. A purulent discharge from the nose is common. The mouth is large and open, and the tongue is also enlarged, showing possible signs of a lingua scrotales. The lips and cheeks appear thickened. The general impression of the face is grotesque and resembles that of the gargoyls of Gothic cathedrals, with their high foreheads, heavy course features, widely spaced eyes, heavy molar regions with huge upper jaw, broad snub noses and long thick upper lip and bulging cheeks. The neck is short and appears to rest directly upon the shoulders. The trunk is short and deformed by kyphosis of the lower thoracic and upper lumbar regions. Deformities of the thorax are present. The sternum has been

described as sunken or bulging, short and flat. The abdomen is long, protuberant and flaccid, and umbilical hernias are common. The extremities reveal a variety of disturbances upon x-ray examination. The joints may be swollen and have limited motion. There may be varus or valgus position of the large joints with the corresponding restriction of motion. The shoulder joints may be most strikingly restricted in all directions, while the elbow and knee joints usually reveal a limitation of extension. The hands are broad and stubby. The fingers are in a flexed to partially flexed position, caused usually by a flexion contracture in the second phalangeal joint, which even passively can be straightened only with difficulty. The terminal phalanges often deviate radially. Depending on carpal bone development, the hand joint may exhibit over-extension or extension and flexion restrictions. Watchglass fingernails are frequently observed. The liver and spleen are enlarged to degrees which may vary during the course of the disease. The muscular development is sometimes found to be poor, and motions are sluggish and weak. The muscles are frequently hypotonic. While symptoms of heart decompensation are absent, signs of mitral insufficiency with systolic murmurs over the apex are frequent. The skin may be abnormally flaccid. A case has been reported in which multiple, symmetrical deep creasings in the feet were noted. Hypertrichose is a frequent sign with increased growth of hair seen especially covering the shoulders, upper part of the arms and the back. Delay of secondary sex characteristics is often striking as are other endocrine dysfunctions. Mental development is poor. Imbecility may be strikingly apparent. The child learns to walk and talk later than usual. Vision may be poor, and there may be signs of decreased hearing accuity even to the degree of deafness. Blood changes (anemia, reduction of hemoglobin, leukopenia or leukocytosis, increase in sedimentation of erythrocytes, delayed coagulation, thrombocytopenia, hemorrhogic phenomenon and decrease of fibrinogen and globulin) may also be features of Gargoylism.

ROENTGENOLOGY

Gargoylism is of all the generalized intrinsic dystrophies of the skeleton third in frequency, The skeletal changes, as disclosed in roentgenograms, are pathognomonic when they are fully developed. Almost all bones of the body may be involved, but the distribution of bone lesions is characteristically uneven. The bones of the leg, in contrast to those of the hands, arms and ribs which most often show

the most marked changes, are little affected, and diagnostic changes rarely develop in them.

The basic lesions in the tubular bones in swelling of the shafts due to expansion of its medullary cavity. The cortical walls are usually thin, but they may be thickened during the first years of life. In addition, the external contours are further deformed by incomplete modelling and tubulation which produce shafts with tapering, pinched-off ends resembling the outlines of sausages, bananas, or bottles (metacarpels). Occasionally, both ends of the shaft remain swollen, and its central segment is constricted in a dummbell shape. This is perhaps the most important single diagnostic change in the skeleton of a patient with Gargoylism, and without this change, the roentgen diagnosis is always uncertain. The roentgen changes at the cartilage shaft junctions and the epiphyseal plates, in contrast, are minimal and are not diagnostic in themselves. Often the epiphyseal plates of the radius and ulna are tipped toward each other, owing to retarded longitudinal growth in the epiphyseal cartilage on the shorter side of each of these shafts.

The paucity of metaphyseal changes and the conspicuous and consistant diaphyseal expansion differentiates Gargoylism sharply from other oesteochondrodystrophies, including Morquios disease, in which the metaphyseal changes are pronounced and diaphyseal expansion is lacking.

Scaphelocephalic skull malformation with a keel like medial ridge extending to the bridge of the nose has been described by Jelke. He also found the parietal bones bulging outward and the temporal bones depressed downward with the result that the pori acustica came to be set low, as was also the outer ear. He believed the cause of these anomalies to be premature closing of some of the sutures and delayed closure of others. Liebenam, Ullrich and Eichenberger have described similar malformations. Hurler, Kottger and Strauss all described the findings of thickened calvariums with unduly prominent vascular channels and anomalies in the closures of the sutures. Jelke, Ullrich and Boldt found the sella turcica shallow and long in the sagittal direction. The clinoid process was thickened and deformed. The ribs, especially the lower ones, were wide with slender neck portions. Zellweger believed this finding to be specific for Gargoylism, while Aegler and Eichenberger are hesitant in placing such great significance to this symptom. A backward subluxation of the second and sometimes of the first lumbar vertebrae is responsible for the typical kyphosis frequently found in Gargoylism. The vertebrae show anterior wedging and are often almost atrophic and malformed, particularly the second lumbar vertebra, which is sometimes displaced backwardly to such an extent that the adjacent anterior part of the first and fourth lumbar vertebrae practically meet one another. The question of whether this condition is pathognomonic

for Gargoylism is still much debated. Reilly and Lindsay attribute this malformation to retarded ossification of the proximal half of the lumbar vertebrae in relation to the distal half. Maldevelopment of the articular processes is probably also partly responsible.

Osteoporosis and delayed ossification centers, are frequently found. Either coxa vara or coxa valga may develop. The proximal thirds of the femoral disphyses are sometimes shrunken to less than half their normal caliber. A tendency to luxations is also described, due to the deformities of the head of the femur.

LABORATORY FINDINGS

The laboratory findings in cases of Gargoylism are relatively scarce, and those that have been reported present an uncharacteristic picture.

Lindsay et al. found one case of Gargoylism with an increased cholesterin value, but were unable to affect any alteration in its amount with either a high or low cholesterin diet. Other cases of Gargoylism have shown values for total fat and phospholipids within normal ranges.

Jelke described a case of Gargoylism in which the oral glucose test gave a flat curve similar to that found in von Gierke's disease. De Lange and Lindsay both reported cases which reveal pathological results of the galactose test. Otherwise reported laboratory tests concerning cases of Gargoylism have not been able to establish any peculiarities which might be helpful as aids in the diagnosis of the disease.

GENETICS

As with many of the other mysteries which remain unsolved in the relatively brief history of this disease, a review of the literature reveals no specific explanation as to the role heredity plays.

Morquio, Ullrich, De Rudder, Schinz, Weidmann, Zellweger and Schaichert believe the disease to be passed by a simple recessive factor. Halperin and Curtis also believed that the disease was due likely to the action of a single recessive autosomal gene. The disease has frequently been described as appearing within families. Böcker related an instance with familial recurrence in which, in line of descent from one woman, there was one boy with dysostosis multiplex in the second generation, a girl with Morquio's Disease and two boys with dysostosis multiplex in the fourth generation. Lindsay found family recurrence in the same generation in five

of thirteen families with dysostosis multiplex. Jelke stated that the disease was reported 18 times in two siblings and twice even in three siblings. He further reported that the disease has been noted in twins. In one pair it was found that only one member was affected. Parents are usually healthy and do not differ in appearance from ordinary phenotypes. A history of consanguinity has been in no way infrequent between the parents or grandparents, which leads again to the consideration of the action of some recessive genetic factor.

Washington and Jelke in their statistics found that 2/3 of cases related of Gargoylism appeared in males, while Fairbank found the relation to be 57 % males to 43 % females. Nja reported the history of a family of 11 children, of which three sons exhibited Gargoylism. The five daughters were of normal appearance, but sons of three of them developed the disease, although none of the cases showed corneal clouding. It was suggested that daughters may have been carriers. Otherwise, the literature has not been able to demonstrate the disease as being sex-linked.

GEOGRAPHIC OCCURRENCE

As the disease has become better known and understood, it is now less considered as exceedingly rare. Its occurrence is widespred, although it has not been reported from the southern hemispheres (Lefebure, Lereque and Gay).

CASE HISTORY

Case: B. S., a girl, born February 22nd, 1945.

Father, at the time when case history was taken, was 37 years of age. In 1937, he suffered a serious attack of poliomyelitis, which left a paralysis of his right leg. Otherwise, he appeared healthy. The mother likewise appeared healthy and had no history of previous serious illness. There was no history of physical or mental peculiarities on either side of the family, or of consanguinity. The child was the first of three children. The two others, a boy and a girl, both are well.

Antenatal development was apparently normal. The mother suffered no infectious diseases during her pregnancy. Delivery was normal, and occurred on the planned termination. The infant's condition at birth was apparently satisfactory. A fleeting icterus neonatorum was described. It was remarked that after the birth, no peculiarities of the child were noted. For the first 6 months, the child received mother's milk. She received only breast feedings for the first two months. From the 4th month on, the child was started on fruits and vegetables.

The first teeth appeared at 10 months. The child sat at about the 10th month and stood at 20 months. Speaking began about the 12th month, but within the past years showed little progress. During the second year, the mother noticed that the child's head was too large and that she would stand slightly bent forward.

The child had no diseases until the second year, when she began to show a tendency to frequent otitis media. There was also a definite tendency to catharrhal infection, which, since the second year, had become chronic and produced an abundant purulent secretion. The child also shows a tendency to diarrhea and is sensitive to fats, especially when taken before bedtime. There is no vomiting; no disorders of the urogenital tract; no infections diseases in the child's surroundings.

The most distressing abnormality noted by the parents, was the child's great difficulty in standing freely and the tendency to carry her strikingly large head resting between her shoulders. Since birth, the parents also observed that the child's ear lobes were swollen and were abnormally striking. Her neck was believed to be short. During her subsequent development, it was also noticed that a certain disproportion between the extremities and body had occurred. It was felt that the upper part of the body was growing more rapidly than the lower part.

Signs leading to the actual clinical picture of the disease developed at the end of the first year: Gargoyl features of the face, large abdomen and also the disproportioned body. With the beginning of the second year, the condition became more serious and further signs were noted: Flexion contractures of the fingers, contracture of the knee-joints, and also clouding

of the corneas. The teeth were small and widely spaced. The hair was bristly, and the skin was delicate, dry, fissured and scaly. The diagnosis of Morbus Pfaundler-Hurler was made by Professor Glanzmann when the child was 1 1/2 years old. At that time, the skeletal x-rays were not yet fully significant. At the age of three, the child was hospitalized for treatment of an umbilical hernia.

The mother stated that the child's intelligence was not much greater than her two years old brother's. However, she played and lived after a certain schedule. Orders could hardly be executed. Emotionally, the child was kind, gentle, and affectionate. She never cried loudly, which was noted by acquaintances even when the child was still a baby.

At 5 1/2 years, the child was admitted to the Jenner Kinderspital, Berne. She revealed the classical appearance of dysostosis multiplex. The child at first whimpered; her voice had rather a toneless quality. The child frequently was noted to hold her right thumb in her mouth, which created an even more peculiar appearance. Most strikingly, her head in relation to her body was very large. The child weighed 17,0 kg and was 101,0 cms tall. The head was large (occipito-frontal circumference 55,0 cms). The anterior posterior diameter of the thorax measured 58,0 cms, and the same diameter of the abdomen over the umbilicus measured 59 cms. The diameter of the joint of the left hand was 12,5 cms.

The skin generally appeared swollen, odematous, shiny and in certain areas was richly covered with lanugo hairs. The skin and subcutaneous tissue had characteristics which were reminiscent of myxedema. Except for reddened areas attributed to scratching and the reddened areas around the nares, there were no pathological efflorescenses to be found. An operation scar for an umbilical hernia was described. An accurate determination of the fatpolster was difficult, due to the oedematous infiltration of the tissue.

The blond hair was brittle and dry. Many of the hairs of the head revealed fractures; others were bent and showed sagittal splitting at their ends.

Typical watchglass nails of the fingers and toes were present.

The body temperature was afebril.

The lymphnodes were enlarged and upon palpation were felt as many small nodes. This was especially striking in the neck region.

The thyroid gland was not palpable. Attempts to palpate the gland revealed merely the trachea.

The skull was coarsely modelled. The bridge of the nose was sunken, the zygomatic processes were prominent, and the maxilla was well developed. The mandible appeared smaller than normal, although it was also well developed. The sutures of the skull, although easily palpable, were closed. The thorax was shortened in its length. It was pectus carinatum in form, with corresponding kyphosis in the region of the thoracic vertebral column. The lumbar region of the vertebral column appeared less affected. The pelvis also revealed slight deformities. The extremities appeared plump, and the epiphysis were slightly widened and partially curved. Especially noticeable were well developed joint contractures, involving practically all joints; certain ones affected to a greater degree than others. The joint between the middle and end phalange of the finger was the most seriously affected, which lead to the appearance of the socalled claw-hand.

The heart action was regular, and the tones were normal. It was not possible to determine its configuration with accuracy. The pulse was regular and full.

An exact examination of the lungs by percussion was made difficult by the various deformities. However, percussion and ascultation revealed no pathological findings.

The abdomen was protuberant and appeared to hang. There was a striking diastasis of the rectus muscle that appeared wide and through which, upon pressing, abdominal contents could be seen to pass.

The liver was easily palpable, firm, and its edges tended to be rounded. It was found extending to 3 fingerbreadths below the costal margin in the mid-clavicular line.

The spleen was likewise enlarged, but to a lesser degree, and could be palpated 2 to 3 fingerbreadths below the costal margin. No abnormal resistance was palpated.

The labia major appeared swollen, but shriveled, and the clitoris was noticeably enlarged. The entrance to the vagina was small.

The child was mentally retarded. She was unable to articulate real words, and when wishing to make herself unterstood, would only manage to articulate unintelligible sounds. She appeared to take part in her environment and would accept cautiously what was offered to her, as if not to damage it. Her toilet habits were well trained. The child possessed certain regularly displayed habits, which she appeared to enjoy and which restricted her in carrying out various orders.

There were neither meningeal nor encephalitic signs. Reflexes were normal and symmetrically equal. Babinski was negative; Oppenheim was positive, more so on the right than left side.

The eyes showed a slight exophthalmus. The corneas appeared cloudy. The pupils reacted to various intensities of light. While both pupils reacted somewhat slowly and not always completely, the reaction of the right pupil appeared better than the left.

The nostrils appeared narrow. There was a constant sero-purulent nasal discharge, caused by a chronic catharrh. Internal inspection revealed a rhinitis anterior and posterior.

The ears were plump and the ear lobes were thick. The auditory canal was long and narrow. The tympanic membrane appeared pulled in and reddened, which, however, could have been the result of frequent washings of the auditory canal. The auditory canals contained a large quantity of cerumen and small hairs which were difficult to remove and also made inspection of the tympanic membranes difficult. The child could hear, but accuity could not be determined.

The lips were thick. The milk teeth were widely separated. The tongue was large and was constantly held between the lips.

The hard palate revealed marked rippling and was strikingly vaulted and arched. The palate extended exceedingly far back. The throat was slightly reddened. The tonsils were of normal size and the uvula was round and plump. The epipharynx was small in size.

ROENTGENOLOGICAL FINDINGS

Anterior posterior diameter of the skull was abnormally wide and pointed. The sutura sagittalis and sutura lambdoides were closed. The vascular channels were not unduly prominent. The root of the nose was abnormally wide. Further details were difficult to distinguish, due to an unclear picture. A picture taken approximately six weeks later showed that the skull had changed but slightly. The occipitofrontal diameter had increased a few millimeters. The os frontale was seen bulging slightly more. A typical, isolated dihiscense of the sutura coronaria was present. The sella turcica was enlarged (measured 2,1: 0,7 cms).

The first five pairs of ribs were normal. Below the fifth, they revealed an increasing tendency of clubbing and thickening with the descent of each pair. The anterior posterior picture of the thoracic and lumbar vertebrae revealed a deviation towards the right side. The upper thoracic and the lower lumbar vertebrae appeared normal. Increasing in the descent from the 8th thoracic vertebra, the contours of vertebrae appeared less distinct. The cranial and caudal vertebral plates were

bulging and jagged, and the bodies appeared as obtuse cones. Definite wedge-shaped vertebrae, frequently seen in Gargoylism, were not present. The left half of the 4th lumbar vertebra was slightly narrowed, which apparently lead to a right deviation of the lower lumbar spinal column. Localized kyphosis of the lower thoracic and upper lumbar vertebrae column was noted. The stage of development of the apophysis-epiphysis and centers of ossification of the bones of the hand were normal. The metacarpal and carpal and to a lesser extent the middle phalangeal bones, due to an expansion of the medullary cavities, appeared swollen. An increase in the compacta was less obvious. The end phalanges appeared much less affected, and some appeared normal. The right hand revealed a similar picture. However, except for the fifth end phalange which appeared normal, the other phalanges were also seen to be swollen. The bones of the upper extremities were short and wide and appeared plump in their medial section. The carpal bones were normal in number, but poorly developed. The distal radial epiphysis was likewise poorly formed. The pelvis was narrowed. The articular surfaces appeared in an upward direction. However, a luxation of the hip joint was not found. The femur was only slightly shorter than normal. A slig it degree of genus valgus was seen. The bones of the lower limbs were short and plump. The development of the bones of the lower extremity appeared to be normal.

Upon ophthalmological examination, the corneas revealed clouding. An examination of the fundus was not possible, due to the cloudy corneas as well as to difficulties encountered with the impatient child.

The Binet-Simon intelligence test gave the following results:

Actual Age	5 8/12 years
Intelligence Age found upon examination	1 year

$$I.Q. = \frac{\text{Intelligence Age}}{\text{actual age}} = \frac{1}{5.6}$$

Bühler-Hetzer Development test:

Actual Age	5 8/12 years	
Developmental Age	1 year	Intelligence 1/5 = 0.2

Lumbal puncture:

Pressure	-	normal
colour	-	at first blood stained, then clear
Pandy	-	positive
Nonne	-	negative
Haine	-	slightly increased 61 mg%
cells	-	2/3; many R.B.C. because of accidental bleeding.

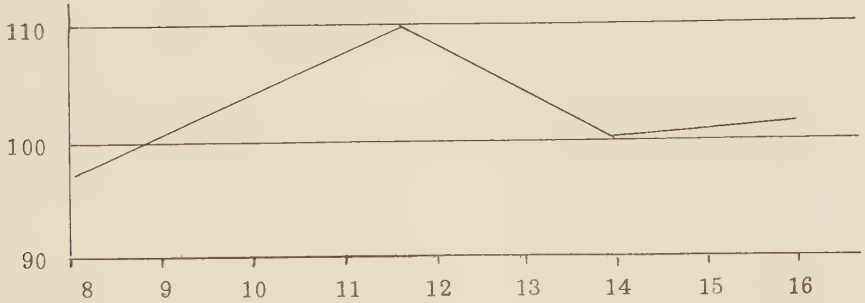
Blood Picture:

	26.9.50	19.10.50	17.11.50
Hb	93	74	77
Erythrocytes	4.7	4.0	3.8
Colour index	.99	.92	1.01
Leucocytes	7'100	6'200	6'300
Red Blood Picture	Normocytes	Normocytes	Normocytes

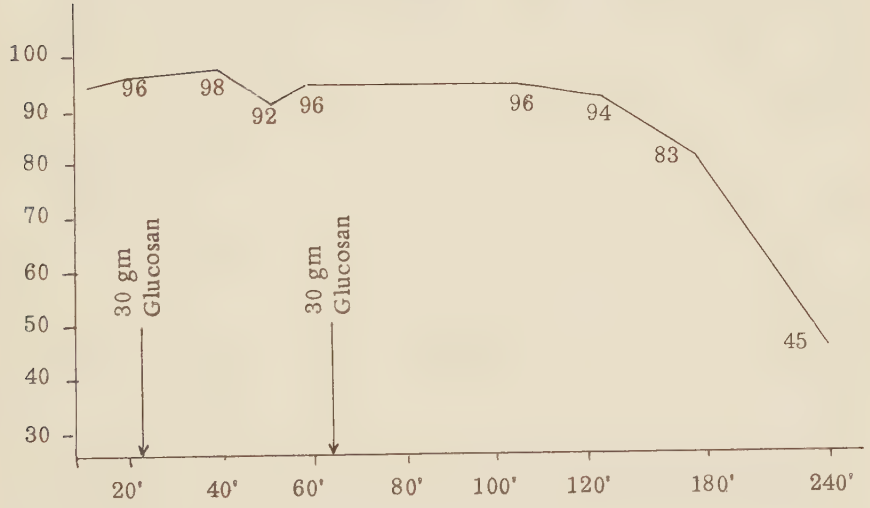
White cell picture in %	26.9.50	19.10.50	17.11.50
Metamyelocytes, staff form nuclei	5,5	0,5	4,5
Segmented nuclei	32,5	47,5	42,0
Eosinophiles	3,5	5,5	3,5
Lymphocytes	55,5	41,5	43,5
Monocytes and transitional forms	3,0	5,0	6,5

	24.11.50	29.10.50
Total cholesterin (150-200 mg%)	160	165.0
Cholesterin - Esters	137,5	114,0
Cholesterin - Esters in % of Total cholesterin (60-80 %)	84 %	69.10
Total Lipoid	1310 mg%	721.2
Total Protein 6-8 %		7.28 %
Serum albumin (5 %)		5.06 %
Serum globulin (2-2.7 %)		2.22
Al/Gl Quotient 1,5 (-2,5)		2.28
Calcium (9-11 mg%)		10.7 mg%
Phosphorus (inorganic) (2-4 mg%)		3.63
Phosphatase (1,5-4 Embe)		5.75

Profile of days Blood Sugar



Two-dose oral glucose tolerance



SUMMARY

Gargoylism is a congenital metabolic disorder. A review of the pathology makes it apparent that the disease is one of abnormal storage in which all tissues of the body may be affected. The abnormal deposit in question and the way in which it is stored remains unproved. The clinical findings described in a variety of cases have revealed a multitude of signs and symptoms. Diagnosis is based upon a variety of clinical components, each of which, however, is not always present in all cases. The skeletal changes, as disclosed in roentgenograms, are pathognomonic when they are fully developed. The laboratory findings present an uncharacteristic picture. A review of the literature reveals no specific explanation as to the role heredity plays, although some connection appears to exist.

One case of a five years old girl is described. Signs leading to the actual clinical picture of the disease developed at the end of the first year. Typical gargoyl facial features, hepatosplenomegaly, corneal clouding, disproportioned body, mental deficiency, flexion contractures of the fingers and knee joints, protuberant abdomen and umbilical hernia, watchglass nails, enlarged lymphnodes, and the diagnostic roentgenologic signs of the disease were present.

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M.G.

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